REMARKS/ARGUMENTS

Claims 1-19 have been deleted. New claims 20-52 are pending in this application. No new matter has been added. Attached hereto is a clean copy of all claims pending in this application marked **"Clean Copy Of All Pending Claims."**

The issues outstanding in this application are as follows:

- The Oath or Declaration is objected to because it does not identify the citizenship of the inventor; it does not indicate the status of Application PCT/GB99/03738.

- Claims 1-4, 7, 9-11, 13, and 15-18 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

- Claims 1-19 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

- Claims 1-5, 8, 9-12, 14, and 18 have been rejected under the judicially created doctrine of obviousness-type double patenting.

- Claim 19 was rejected under 35 U.S.C § 102(b) as being anticipated by Düwel *et al.*(1975; U.S. Patent No. 3,888,978).

- Claims 1-5, 9-12, and 18 and 39 have been rejected under 35 U.S.C. § 103(a) as being obvious over Errington (1997; WO 97/00325) in view of Hodgson *et al.* (U.S. Patent No. 5,891, 667) and in further view of King *et al.* (WO 92/05244).

Applicants respectfully traverse the outstanding rejections and Applicants respectfully request reconsideration and withdrawal thereof in light of the remarks contained herein.

I. A corrected oath is submitted.

The Applicant herewith submits a new oath that complies with CFR 1.67(a), that correctly identifies the citizenship of the inventor and the status of Application PCT/GB/03738.

II. 35 U.S.C §112 first paragraph, written description rejection.

Claims 1-4, 7, 9-11, 13, and 15-18 have been rejected under 35 U.S.C §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses.

Claims 1-4, 7, 9-11, 13, and 15-18 have been deleted. New claims 20-52 are adequately supported by the written description.

Independent claim 20 is to a Bacillus strain where the endogenous *spoIIIE* gene is replaced by a homologous gene from another bacterium. Independent claim 42 is to a Bacillus strain in which the *spoIIIE* gene is nonfunctional. The Applicant notes that the Bacillus strain of claim 20 carries a functional *spoIIIE* gene, and thus exhibits the wild-type *spoIIIE* phenotype. The Examiner's definition of the *spoIIIE*-like phenotype is a bacterium that does not express a functional *spoIIIE* gene. The Applicant hereby clarifies the definition of *spoIIIE* phenotype as comprising both a strain as described in claim 20 as well as a strain as described in claim 42. The strain of claim 20 does not exhibit the unique sporulation phenotype described by the specification on page 5, line 14, until the homologous gene product has been rendered nonfunctional, for example by an antibiotic. In the case of claim 42, the Bacillus strain has been modified such that the native *spoIIIE* gene is nonfunctional. A nonfunctional *spoIIIE* gene, such as in claim 42 also gives rise to a strain which exhibits trapping of the prespore chromosome. The Examiner has stated that the written description supports a claim to Bacillus strains with a *spoIIIE*-like phenotype, but the Applicant also notes that the written description includes both strains with a wild-type *spoIIIE* phenotype, as well as strains with the unique sporulation phenotype that is the result of a nonfunctional

spoIIIE gene. Claims 20 and 42, and subsequent dependent claims, are to such strains as the Examiner readily admits are supported by the written description.

The Examiner has also stated that the third representative species provided a means to assay the activity of σ^F or σ^E function. Independent claim 31 is to a Bacillus strain in which σ^F or σ^E function can be assayed. As outlined in the description at page 7, lines 11 to 24, synthesis of σ^F begins at the outset of sporulation. However σ^F is held in an inactive complex initially and is only released after asymmetric cell division, when σ^F activity can be identified to the smaller prespore cell type. σ^F activity is therefore dependent on cell division. Inhibition of a gene involved in cell division will affect σ^F activity.

Claim 31 comprises a reporter gene which is expressed at the same level as σ^F and thus provides a measure of σ^F synthesis. The second reporter gene is dependent on σ^F activity and is only active once σ^F is released from the complex. Thus the second reporter gene is only expressed when cell division is possible. Thus it is clear that the assay system can be used to measure whether or not a gene essential for cell division is impaired or not. If only the first reporter gene is expressed, it can be deduced that gene expression generally has not been impaired, and that the inhibition of the second reporter gene expression is attributable to inhibition of cell division.

The specification therefore adequately describes each of independent claims 20, 31, and 42, as well as their subsequent dependent claims. The Applicants respectfully request that the 35 U.S.C 112 written description rejection be withdrawn.

III. Pending claims do not contain indefinite language.

Claims 1-19 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Claims 1-19 have been deleted. The Examiner correctly remarked that Claim 1, and all claims depending from claim 1, were indefinite because of use of the indefinite article "a" preceding "homologous gene expression product" in claim 1. Pending claims 20-52 contain no indefinite language as found in deleted claim 1.

Claim 2 was additionally rejected for indefiniteness due to the use of the phrase "involved in", which the Examiner interpreted as indefinite language. The Applicant has deleted claim 2, thus rendering the rejection moot.

Claim 12 was rejected for indefiniteness due to the misspelling of SpoIIIE. This claim has been deleted, and all new claims include the correct spelling of SpoIIIE, and are not indefinite. Support for the correct spelling of SpoIIIE is found on page 2, line 26.

Claim 18 was rejected for indefiniteness for the lack of a preamble recitation. Claim 18 has been deleted. Pending claims 20-52 contain no indefinite language as found in deleted claim 18.

IV. Absence of double patenting.

Claims 1-5, 9-12, and 18 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 6, and 9 of U.S. Patent No. 6,027,909 in view of Hodgson *et al.* (U.S. Patent No.5,891,667) and in further view of King *et al.* (WO 92/05244). Claims 1, 3, 4, 8 and 14 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 6,350,587 in view of Jaworski *et al.* (U.S. Patent No. 6,080,729) and in further view of King. Applicants respectfully traverse. Any analysis employed in an obvious-type double patenting determination parallels the guidelines for a 35 U.S.C. § 103(a) rejection. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991).The MPEP sets forth the guidelines to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a) (MPEP § 2143.3). Three basic criteria must be met to establish a *prima facie* case of obviousness. The three criteria are:

> 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> 2) a reasonable expectation of success; and

3) the prior art references must teach or suggest all the claim limitations.

In light of the above criteria, Applicants assert that the Office has not established a *prima facie* case of obviousness to reject the claims under 35 U.S.C. § 103. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, (Fed. Cir. 1991). A prima facie case necessitates disclosure of the source for either a suggestion or motivation to modify a reference to produce the present invention, and a reasonable expectation of success of producing the present invention. A *prima facie* case must be established by evidence rather than conjecture. *Ex parte Yamamoto*, 57 USPQ2d 1382, 1383, 1384 (CCPA 2000).

(i) US Patent 6,027,909 in combination with Hodgson *et al* (US Patent 5,891,667) and/or King *et al* (WO/92/05244)

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) There is no motivation to combine Errington, Hodgson, and King. Hodgson *et al* teaches the cloning of *spoIIIE* from *S. aureus*. Hodgson *et al* refers to expression of recombinant *S. aureus spoIIIE* in other cell types. However, the production of the strains of claim 20 for use in the assays of the invention is not obvious from Hodgson, as Hodgson does not teach strains with the reporter genes specified by claim 20. Discussion of expression of heterologous genes in Hodgson *et al* is always in the context of protein expression to produce recombinant protein and not in relation of an assay. None of the assays that are mentioned in Hodgson *et al* involve heterologous expression and it is therefore apparent that the possibility of such assays is not suggested or taught by Hodgson.

The Examiner cites the passage in Hodgson *et al* (column 1, lines 16 to 19) where it is stated that it is preferred to employ staphylococcal genes as targets for the development of antibiotics as providing motivation to combine US Patent 6,027,909 with Hodgson *et al*. This passage is merely stating that staphylococci are medically important pathogens and hence it is desirable to produce therapeutic agents against them. It is not an indication to study a staphylococcal gene in a Bacillus, but would suggest that staphylococcal assay systems using staphylococci should be used. The statement in Hodgson *et al* that *spoIIIE* is

conserved between species is also not a suggestion to study the gene from one organism in another. Therefore, there is no motivation to combine Hodgson with Errington.

The Examiner also cites a passage in US Patent 6,027,909 that the unique phenotype arising when SpoIIIE is inactivated gives rise to the possibility of a powerful assay (column 2, lines 30 to 35) as providing motivation to combine US Patent 6,027,909 with the other documents. However, this passage merely indicates that the unusual phenotype resulting from impairing SpoIIIE function gives rise to a convenient way to assay for activity through positioning of the reporter genes appropriately. It is not an indication that a heteologous gene could be introduced into the strains of the assay or to do anything beyond studying the activity of the endogenous *spoIIIE* gene in its natural context i.e. to study the Bacillus *spoIIIE* gene in the Bacillus itself. This passage does not offer motivation to combine any of the prior art documents with US Patent 6,027,909 as there is no suggestion of a need for alternative assays.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Whereas the purpose of the assay of US Patent 6,027,909 is to study the activity of SpoIIIE from the endogenous *spoIIIE* gene of the Bacillus, the purpose of the assays of the present invention is to study the function of SpoIIIE from a *spoIIIE* gene of another bacteria in the Bacillus system. As such, the Bacillus strain of claim 20 has the endogenous *spoIIIE* gene replaced with a heterologous *spoIIIE* gene. US Patent 6,027,909 is to with an assay in which the expression of two reporter genes in a *Bacillus* strain is dependent on the activity of the endogenous *spoIIIE* gene. If active endogenous SpoIIIE is present, then the bacterial chromosome successfully reaches the prespore compartment, both reporter genes are exposed to the transcription factor σ^F and both are expressed. If endogenous SpoIIIE activity is impaired, then only part of the bacterial chromosome carrying a single reporter gene reaches the prespore compartment, hence only one reporter gene is exposed to σ^F and is expressed.

The assays of the present invention are not taught by US Patent 6,027,909, nor by US Patent 6,027,909 in combination with Hodgson and King.

(ii) US Patent 6,350,587 in combination with Jaworski *et al* (US Patent 6,080,729) and/or King *et al* (WO/92/05244)

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) As in the case of Hodgson *et a,* all discussion of heterologous expression in this document is in the context of producing recombinant protein and there is no suggestion of studying the function of SpoOJ from a different organism in Bacillus. There is no suggestion in Jaworski that it would be desirable to study heterologous expression in any assay as taught by Applicant. U.S. Patent No. 6,350,587 provides no suggestion that such a combination is desirable. The prior art references do not suggest a motivation to combine. The motivation to combine Errington, Jaworski, and King may not come from Hodgson, who is not cited in the double patenting rejection over U.S. Patent No. 6,350,587.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Jaworkski *et al* teaches the cloning of the *S.aureus* homologue of the *spoOJ* gene. In the written description, the Applicant teaches target homologous genes of a wide variety of functions, not just the *spoOJ* gene. These limitations are described on page 7, lines 25-30. Additionally, applicants teach methods for determining whether an agent inhibits the growth of a bacteria, as well as teaching a panel of *spoOJ* gene replacements from many different original bacteria sources.

US Patent 6,350,587 teaches an assay involving a strain of Bacillus in which *spoIIIE* has been inactivated and examines the activity of the endogenous *spoOJ.* As the strain lacks

a functional *spoIIIE* gene the bacterial chromosome only partially enters the prespore. SpoOJ influences which part of the chromosome is trapped in the prespore and if it is inactive the orientation of the chromosome is more random. By positioning the two reporter genes appropriately, this means the activity of SpoOJ can be determined. However, as in the case of US Patent 6,027,909 discussed above, the gene whose function is being studied is an endogenous one, native to the Bacillus strain and not, as specified in claim 42, a heterologous gene. Accordingly, as outlined above for US Patent 6,027,909, there is no reason why the skilled person would be led to produce a Bacillus strain where the endogenous locus had been inactivated and replaced with a homologue. These limitations of the claimed invention are not taught or suggested by the prior art, and thus a prima facie obviousness has not been established.

In light of the above arguments, Applicant respectfully requests withdrawal of the double patenting rejection.

V. 35 U.S.C. 102(b) anticipation by Düwel *et al.*

Claim 19 was rejected under 35 U.S.C. 102(b) as being anticipated by Düwel *et al.* (1975; U.S. Patent No. 3,888,978). The Examiner noted that claim 19 does not distinguish between compounds that are capable of killing a bacterium and those compounds that specifically act on the product of the homologous gene. Claim 19 has been deleted. New claims 30, 41, and 52 are written to a method of killing or inhibiting the growth of bacteria with an agent which acts on the homologous gene product of the bacteria of claims 20, 31, or 42. Claims 30, 41, and 52 have been limited in its scope to specifically designate only those compounds identified by claims 29, 40, and 51 respectively.

VI. Pending claims 20-52 are nonobvious

The Examiner states that the disclosure of Errington (WO97/00325) is equivalent to US 5,891,667. It is assumed that this is a typographical error as US 5,891,667 is Hodgson *et al.* It is assumed that the Office Action meant to refer to US Patent 6,027,909 which does

name Errington and is the US national phase of WO97/00325.

The Examiner has rejected claims 1-5, 9-12, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Errington in view of Hodgson *et al.* (U.S. Patent No.5,891,667) and in further view of King *et al.* (WO 92/05244). The Applicants respectfully traverse for the same reasons as outlined in the arguments traversing the obvious-type double patenting rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant submits herewith a check in the amount of $72 to cover charges incurred by additional claims. In addition, Applicant submits herewith a check in the amount of $55 for a one month extension of time. Applicant believes no additional fees are due. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02186US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

By 

Thomas D. Paul
Registration No.: 32,714
FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
(713) 651-5151
(713) 651-5246 (Fax)
Attorneys for Applicant